REMARKS

Upon entry of the foregoing amendments, amended claims 1, 5, 6, 10, 11, 13 and 15-18 will be pending. Claim 1 is the only independent claim. Claims 2-4, 7-9, 12 and 14 are cancelled without any prejudice or any disclaimers.

The specification has been thoroughly amended as requested by the Examiner to correct typographical and grammatical errors, to clarify the invention disclosure so as to place the present application in a more readable form. Therefore, no new matter is added when the specification is amended.

Applicants have also submitted an Amended Sequence Listing to replace the previously amended sequences of SEQ ID NOs: 1 - 15 in the sequence listing filed on August 30, 2004. Therefore, the new matter allegedly introduced as a result of previously filed amended SEQ ID NOs: 1, 2, 13 and 14 has been cancelled and the original sequence listing is restored. Since the accompanying Amended Sequence Listing is identical to the original Sequence Listing, it is clearly supported by the application as filed.

Claims 1, 5, 6, 11, 13 and 15-18 are currently pending in this application, as amended or newly added. Claims 1 and 13 have been amended to more particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. Support for the claim amendments can be found, in the original specification. Specifically, for example, the grounds for amending claims 1 and 13 can be found from page 4, lines 8-11; page 9, lines 6-11; page 11, lines 9-12; page 17, lines 5-11; page 18, line 25, to page 19, line 5; Example 2; and from the statements in Applicant Chen's Declaration, entitiled "Declaration of Chuan-Mu Chen Under 37 C.F.R. § 1.132" ("Dr. Chen's Declaration") submitted along with the present Amendment. . Claims 5 and 6 as amended and new claim 18 are based on support found on page 11, lines 6-14. Support for amended claim 11 can be found on page 11, lines 9-12, and Dr. Chen's Declaration. Claims 15-17 are amended to correct informalities. Accordingly, no new matter has been added.

Objections to Specification

The amended specification as filed on August 30, 2004 were objected to under 35 U.S.C. 132(a) because it allegedly introduced new matter into the disclosure. Applicants have re-submitted the original sequence listing along with Dr. Chen's Declaration to show that the information provided is true and fully supported by the scope of the invention as originally disclosed in the application as filed. Upon entry of the above amendments, additional typographical and grammatical errors and unclear language are corrected. Reconsideration and withdrawal of the objections to the specification are respectfully requested.

Claim objections

Claims 2, 5, 6, 11, 12, 15 and 17 were objected to because of the informalities as listed on page 4 of the Office Action. Applicants have amended the claims asa set forth above to place the claims in a more comprehensible form. Therefore, Applicants respectfully request that the claim objections be withdrawn.

Double Patenting rejection

Claims 1, 2, 4, 7 and 8 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-9 of copending Application No. 10/727,145 (the "'145 application").

Claim 1 is amended to recite "a genome comprises a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID NO: 15, wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland-specific signal peptide sequence; a nucleotide sequence encoding a signal peptide comprising bovine α-lactalbumin of SEQ ID NO: 13 or bovine α-S1 casein peptide of SEQ ID NO: 14, added to a N-terminal of the B-domain deleted hFVIII polypeptide of SEQ ID NO: 15; and an α-LA promoter", which is now clearly different from claims 6-9 of the'145 application, and claims 2, 4, 7 and 8 are cancelled. Therefore, the double patenting rejection is respectfully traversed in light of the claim amendments above. Reconsideration and withdrawal of the double patenting rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 101

Claims 1-7 and 9-17 have been rejected under 35 U.S.C. § 101 because the claimed invention was assertedly directed to transgenic humans which belong to a non-statutory subject matter.

In light of the claim amendments made above, claim 1, the only independent claim, has been amended to recite non-human transgenic animals including mice, rats, goats, sheep, pigs and cows. Therefore, for at least the claim 1 amendment, the present application is now in condition to overcome the rejection under 35 U.S.C. § 101. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-7 and 9-17 have been rejected under 35 U.S.C. § 112, first paragraph, because in the Examiner's opinion, the specification does not reasonably provide enablement for <u>any</u> transgenic animal whose genome comprises a nucleotide sequence encoding a human FVIII protein or B-domain deleted human FVIII protein, wherein said human FVIII protein or B-domain deleted human FVIII protein is secreted in milk when said <u>any</u> transgenic animal is lactating; and a method of making said <u>any</u> transgenic animal.

Applicants have amended the claims to recite a non-human transgenic animal and a method of making that non-human transgenic animal which is selected from the group consisting of mice, rats, goats, pigs, sheep and cows. Therefore, upon entry of the claim amendment, it is believed that the claims are now fully supported and enabled by the specification. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-17 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants have respectfully submitted the claim amendments above to better define the scope of the invention and correct the typographical errors and grammatical inconsistencies throughout the claims. It is believed that the claims are now in condition for overcoming the

rejections under 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 102(b)

Claims 1-4, 8, 10, 12, 13, 14 and 17 have been rejected under 35 U.S.C. §102(b) as being anticipated by Lubon *et al.* U.S. Patent number 6,255,554 (hereinafter, "Lubon").

Withdrawal of the rejection of the pending claims 1, 5-6, 10, 11, 13 and 15-17 is respectfully requested in view of the foregoing amendments and for at least the following reasons.

i) Claim 1

Claim 1, as amended, recites, *inter alia*:

> A non-human transgenic animal whose genome comprises a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID: NO. 15, a nucleotide sequence encoding a signal peptide comprising bovine α-lactalbumin, and an α-LA promoter, ...

[Underline emphasis added]

Lubon fails to disclose or suggest the genome as defined in the amended claim 1.

Lubon is directed to a transgenic non-human mammal expressing human coagulation factor VIII and von Willebrand factor. More particularly, Lubon is directed to a transgenic non-human mammal having stably integrated into its genome an exogenous double stranded DNA sequence encoding the human Factor VIII (see, for example, claims 1, 4 and 5), a nucleic acid from mouse whey acidic protein (WAP) gene promoter (see, for example, claim 3 in Lubon) and a nucleic acid encoding a secretion signal peptide from WAP (see, for example, col. 6, lines 45-56). The object of Lubon is to provide an efficient means of producing large quantities of human FVIII protein suitable for clinical use. See column 2, lines 42-45.

As discussed in the present application (see page 4, lines 3-11), the full length FVIII cDNA encodes for a 256-kDa precursor human FVIII protein, which is processed to a metal ion-

linked hetero-dimer containing a heavy chain (A1-A2-B domains) and a light chain (A3-C1-C2 domains), which circulate in the plasma and are bound to the von Willebrand factor. However, the B-domain, which is highly glycosylated, harboring 19 of the 25 N-linked glycosylation sites, is released upon co-factor activation and is not necessary for clotting function. Accordingly, Applicants disclose a genome comprising a nucleotide seuquence which encodes B-domain-deleted hFVIII of SEQ ID: NO. 15 (See Example 2 and corresponding Figs. 3A to 3C). Also, the B-domain deleted human FVIII of SEQ ID: NO. 15 is clearly different from the precursor hFVIII protein bound to von Willebrand factor.

A claim is anticipated under 35 U.S.C. §102 only if each and every element as set forth in the claim is found expressly or inherently described in a single prior art reference and the elements must be arranged as recited in the claim. MPEP §2131.

Independent claim 1 has been amended to recite that the genome comprises a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland-specific signal peptide sequence, a nucleotide sequence encoding a signal peptide comprising bovine α-lactalbumin or bovine α-S1 casein peptide added to a N-terminal of the B-domain deleted hFVIII polypeptide, and an α-LA promoter. In contrast, the nucleic acid construct pointed to by the Examiner in Lubon encodes mouse WAP promoter, intact human Factor VIII and human von Willebrand Factor, and WAP protein. The nucleic acid construct is integrated into the transgenic animal to express intact human Factor VIII and human von Willebrand Factor in the milk of the transgenic animal. Therefore, the human clotting factor VIII (FVIII) polypeptide with the B-domain deleted would not be expressed by the nucleic acid construct in Lubon.

It is therefore respectfully submitted that claim 1 is not anticipated by Lubon because Lubon does not disclose or suggest each and every element of claim 1. Claim 5-6 and 9-12 depend either directly or indirectly from independent claim 1. Accordingly, Applicants respectfully request that the rejection of claims 1, 5, 6 and 10 under 35 U.S.C. §102(b) be withdrawn. Claim 18 further defines the α-LA promoter of claim 1 as a 2.0-kb bovine α-LA

promoter. Therefore, claim 18 also patently distinguishes from Lubon for at least the same reasons applied to claim 1.

ii) Claim 13

Claim 13, as amended, recites:

> A method for making said non-human transgenic animal of claim 1 comprising the steps of:
>
> i. introducing into an embryo of the non-human transgenic animal a transgene whose genome comprises (a) a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID NO: 15, wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland-specific signal peptide sequence, (b) a nucleotide sequence encoding a signal peptide comprising bovine α-lactalbumin (α-LA) of SEQ ID NO: 13 or bovine α-S1 casein peptide of SEQ ID NO: 14, added to a N-terminal of said B-domain deleted hFVIII polypeptide of SEQ ID NO: 15, and (c) an α-LA promoter;
>
> ii. implanting the embryo into a female of the same species of the non-human transgenic animal;
>
> iii. permitting the embryo to develop to full term; and
>
> iv identifying the non-human transgenic animal producing milk that contains a detectable quantity of the B domain-deleted human FVIII polypeptide.

[Underline emphasis added]

As mentioned above with respect to claim 1, Lubon fails to disclose or suggest a genome comprising a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID NO: 15, wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland-specific signal peptide sequence, a nucleotide sequence encoding a signal peptide comprising bovine α-lactalbumin of SEQ ID NO: 13 or bovine α-S1

casein peptide of SEQ ID NO: 14, added to a N-terminal of the B-domain deleted hFVIII polypeptide of SEQ ID NO: 15, and an α-LA promoter. Lubon teaches the nucleic acid construct for encoding mouse WAP promoter, human Factor VIII and human von Willebrand Factor, and WAP protein. Therefore, the nucleic acid construct in Lubon would not express the human clotting factor VIII (FVIII) polypeptide with B-domain deleted. It is therefore respectfully submitted that claim 13 is not anticipated by Lubon because Lubon does not disclose or suggest each and every element of claim 13. Claims 15-17 depend from claim 13 and are patentable for the same reasons as stated concerning claim 13.

Applicants respectfully request that the rejection of claims 1, 5, 6, 10, 11, 13 and 15-17 under 35 U.S.C. §102(b) over Lubon be reconsidered and withdrawn.

Claims 1-3, 8, 13, 14 and 17 have also been rejected under 35 U.S.C. §102(b) as being anticipated by Paleyanda et al. (**Nature Biotechnology**, 15: 971-975, 1997; hereinafter, "Paleyanda").

In view of the foregoing amendments and the following reasons, it is respectfully requested that the rejections for the pending claims 1, 13, 14 and 17 be withdrawn.

Paleyanda is directed to a transgenic pig that expresses full-length hFVIII protein as a secretion product in milk and a method of making the transgenic pig. Paleyanda teaches a nucleic acid construct with which the transgenic pig was constructed comprising a nucleic acid encoding full length hFVIII protein, a nucleic acid from the mouse WAP gene polyadenylaltion signal and a nucleic acid from the mouse WAP gene promoter that drives the mammary gland-specific gene expression.

However, Paleyanda does not disclose or suggest a genome comprising the nucleotide seuqnece encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SED ID NO: 15, wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland-specific signal peptide sequence, a nucleotide sequence encoding a signal peptide comprising at least one of bovine α-lactalbumin of SEQ ID NO: 13 or bovine α-S1 casein peptide of SEQ ID NO: 14, added to a N-terminal of the B-domain deleted hFVIII

polypeptide of SEQ ID NO: 15, and an α-LA promoter as recited in the amended claim 1. Paleyanda also fails to teach or suggest a method for making the non-human transgenic animal having a genome comprising a nucleotide sequence encoding a B domain-deleted human FVIII polypeptide of SEQ ID NO: 15, wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland-specific signal peptide sequence, a nucleotide sequence encoding a signal peptide comprising at least one of bovine α-lactalbumin of SEQ ID NO: 13 or bovine α-S1 casein peptide of SEQ ID NO: 14, and an α-LA promoter as recited in the amended claim 13.

Therefore, the human FVIII polypeptide with B-domain deleted would not be obtained by the transgenic pig or method of making the transgenic pig described in Paleyanda. For at least the foregoing reasons, claims 1 and 13 can patently distinguish over Paleyanda. The dependent claims 17 and 18 are also not anticipated by Paleyanda for the same reasons applied to claims 1 and 13. Accordingly, Applicants respectfully request the rejection of the claims under 35 U.S.C. § 102(b) over Paleyanda be reconsidered and withdrawn.

The office action further rejected claims 1-5, 7-9, 11, 13, 14, 16 and 17 under 35 U.S.C. §102(b) as being anticipated by Chen et al. (**Transgenic Research**, 11: 257-268, 2002; hereinafter, "Chen").

Withdrawal of the rejection of the pending claims 1, 5, 11, 13, 16 and 17 is respectfully requested in view of the foregoing amendments and for at least the following reasons.

Chen is directed to a transgenic mouse that expresses full length hFVIII protein as a secretion product in milk and a method of making the transgenic mouse. However, Chen fails to disclose or suggest the genome as defined in the amended claims 1 and 13. Chen merely discloses a nucleic acid construct comprising a nucleic acid encoding hFVIII, a nucleic acid encoding the secretion signal peptide from the α-LA gene, a nucleic acid from the bovine growth hormone gene polyadenylation signal and a nucleic acid from the bovine α-lactalbumin gene promoter in the transgenic mouse and a method of making the transgenic mouse for expressing hFVIII protein in the milk from the resultant lactating transgenic mice. The hFVIII protein is NOT the B-domain deleted hFVIII polypeptide of SEQ ID NO: 15. It is therefore respectfully submitted that claims 1 and 13 are <u>not</u> anticipated by Chen because Chen does not disclose or

suggest each and every element of claim 1 or 13. Accordingly, Applicants respectfully request the rejection of claims 1 and 13 under 35 U.S.C. §102(b) over Chen be reconsidered and withdrawn. For at least the same reasons, it is respectfully submitted that dependent claims 5, 11, and 16-18 are also not anticipated by Chen.

Claims 1, 2, 4, 7 and 8 have been rejected under 35 U.S.C. §102(e) as being anticipated by the copending '145 application, which has a common inventor with the present application.

For at least the foregoing amendments, it is respectfully requested that the rejection for the pending claim 1 be withdrawn.

Upon entry of the amendment, claim 1 now recites "A non-human transgenic animal whose genome comprises a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID NO: 15, wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland-specific signal peptide sequence, a nucleotide sequence encoding a signal peptide comprising bovine α-lactalbumin of SEQ ID: NO. 13 or bovine α-S1 casein peptide of SEQ ID NO: 14, added to a N-terminal of the B-domain deleted hFVIII polypeptide of SEQ ID NO: 15, and an α-LA promoter,..." In contrast, claims 6-9 of the '145 application are drawn to a transgenic animal whose genome comprises a nucleic acid encoding hirudin. The '145 application does not teach or suggest the genome as defined in the amended claims 1 and 13. Accordingly, it is respectfully submitted that claim 1 is not anticipated by the '145 application. Applicants respectfully request the rejection of claim 1 under 35 U.S.C. § 102(e) be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. § 103(a)

i) Rejection of Claims 6, 10, 12 and 15

Claims 6, 10, 12 and 15 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Chen in view of Soukharev et al. (Blood Cells, Molecules and Diseases, 28: 234-248, 2002; hereinafter "Soukharev"), DeBoer et al. (US patent 5,633,076, hereinafter "DeBoer") and Lubon.

Withdrawal of the rejections of pending claims 6, 10 and 15 is respectfully requested in view of the foregoing amendments and for at least the following reasons.

Claims 6 and 10 depend from independent claim 1.

As set forth above with respect to independent claim 1, Chen fails to disclose or suggest the genome comprising a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (hFVIII) polypeptide of SEQ ID NO: 15, wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland-specific signal peptide sequence, a nucleotide sequence encoding a signal peptide comprising bovine α-lactalbumin of SEQ ID NO: 13 or bovine α-S1 casein peptide of SEQ ID NO: 14, added to a N-terminal of the B-domain deleted hFVIII polypeptide of SEQ ID NO: 15, and an α-LA promoter. This is also evident from Example 2 of the application, where the B-domain deleted hFVIII transgene construct was driven by α-LA promoter and α-S1 casein secretory peptide sequence. The α-S1 casein secretory peptide with 15 amino acids was added in N-terminal of the hFVIII polypeptide for leading the newly synthesized hFVIII secretion into mammary ductal cavity.

Soukharev assertedly provides a teaching of "removal of the B-domain to dramatically improve the yield of FVIII" to modify the hFVIII expressing transgenic mouse of Chen. Deboer assertedly provides a teaching of "said various nucleic acid elements to include a nucleic acid encoding α-S1 casein secretion signal peptide operably linked to a nucleic acid encoding said recombinant protein specifically for the purpose of promoting secretion of said recombinant protein in the milk of the transgenic animal". However, there is no teaching, suggestion or motivation in either Chen, Soukharev, DeBoer or Lubon to add the signal peptide, particularly bovine α-S1 casein of SEQ ID NO: 14 to a N-terminal of said B-domain deleted hFVIII polypeptide of SEQ ID NO: 15. Therefore, even if the cited prior art references are combined, the combination still fails to teach or suggest each and every element of claim 1.

In contrast, in Applicants' invention the expression of B-domain deleted hFVIII polypeptide in the milk of non-human transgenic animal driven by bovine α-lactalbumin seems more efficient than other transgene constructions. Use of bovine α-lactalbumin and bovine α-S1 casein to lead the B-domain deleted hFVIII polypeptide secretion also contributes to the success

of temporal expression of hFVIII in the milk of the non-human transgenic animal without exerting other biological effects to the transgenic animals (see page 16, line 24, to page 18, line 1). Therefore, without a teaching or even a hint of "adding the signal peptide to a N-terminal of said B-domain deleted hFVIII polypeptide of SEQ ID NO: 15", claim 1 is non-obvious over the cited prior art, even in combination. Claim 15 depends from claim 13, which has the same elements as claim 1. In view of the foregoing reasons, dependent claims 6, 10 and 15 are also patentable over Chen in view of Soukharev, DeBoer and Lubon.

Applicants therefore respectfully request that the rejection under 35 U.S.C. § 103(a) with respect to claims 6, 10 and 15 be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, it is respectfully submitted that the present application, including claims 1, 5, 6, 10, 11, 13 and 15-18, is in condition of allowance and such action is respectfully requested.

Respectfully submitted,

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By: 

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